Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial

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Summary

Background **Traumatic brain injuries represent an important and costly health problem. Supplemental magnesium positively affects many of the processes involved in secondary injury after traumatic brain injury and consistently improves outcome in animal models. We aimed to test whether treatment with magnesium favourably affects outcome in head-injured patients.**

Methods **In a double-blind trial, 499 patients aged 14 years or older admitted to a level 1 regional trauma centre between August, 1998, and October, 2004, with moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within 8 h of injury and continuing for 5 days. Magnesium doses were targeted to achieve serum magnesium ranges of 1·0–1·85 mmol/L or 1·25–2·5 mmol/L. The primary outcome was a composite of mortality, seizures, functional measures, and neuropsychological tests assessed up to 6 months after injury. Analyses were done according to the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT00004730.**

Findings **Magnesium showed no significant positive effect on the composite primary outcome measure at the higher dose (mean=55 average percentile ranking on magnesium *vs* 52 on placebo, 95% CI for difference –7 to 14; p=0·70). Those randomly assigned magnesium at the lower dose did significantly worse than those assigned placebo (48 *vs* 54, 95% CI –10·5 to –2; p=0·007). Furthermore, there was higher mortality with the higher magnesium dose than with placebo. Other major medical complications were similar between groups, except for a slight excess of pulmonary oedema and respiratory failure in the lower magnesium target group. No subgroups were identified in which magnesium had a significantly positive effect.**

Interpretation **Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.**

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Introduction

Traumatic brain injuries are common and represent an important and costly health problem. The affected population includes many previously healthy young people. Moreover, these injuries are associated with high mortality and morbidity.[1] The pathophysiology of severe brain injury involves a primary event and commonly a subsequent cascade of insults. The primary event is not treatable, whereas the secondary cascade substantially contributes to morbidity and mortality and thus is theoretically amenable to treatment. This theory has encouraged investigators to explore new treatment options and search for the "zauberkugel" or "magic bullet".[2]

Evidence has suggested that magnesium could play a central part in the pathophysiology of traumatic brain injury.[3] Magnesium can protect neurons from ischaemic damage and can support neuronal survival after traumatic brain injury through various mechanisms, including inhibition of the release of presynaptic excitatory neurotransmittors, blocking of NMDA channels and voltage-gated calcium channels, potentiation of presynaptic adenosine, and suppression of cortical spreading depression. Additionally, magnesium causes vascular smooth muscle to relax, thereby potentially increasing cerebral blood flow. After head injuries in human beings, total serum and ionised magnesium concentrations decrease.[4] Experimentally, studies from several laboratories[5] have documented that serum magnesium and brain magnesium are decreased after experimental traumatic brain injury[6] and that magnesium supplementation improves outcome whether given before, shortly after, or hours after injury.[7,8] Outcome is worst in brain-injured animals with artificially lowered magnesium concentrations, intermediate in animals with no intentional alteration in magnesium concentrations, and best in animals given supplementary doses of magnesium. Treatment with magnesium can be successful when it is given up to 24 h after the injury and when given as a single bolus or for up to 7 days.[9] Similarly, in vitro paradigms of neuronal injury and post-traumatic seizures have shown that magnesium concentrations correlate with improved tissue survival and lessened neurological excitation.[10,11]

Our study was designed to test the notion that treating head-injured patients with magnesium would improve outcome. The primary hypothesis was that magnesium

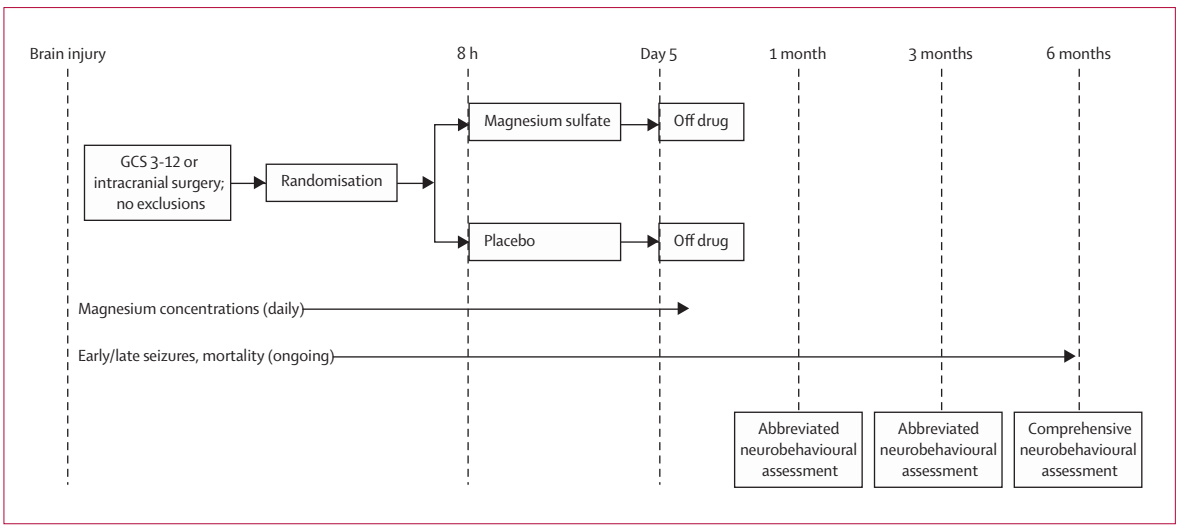

***Figure 1*: Study schema**

sulfate, given within 8 h of moderate or severe head injury, improves a composite measure of survival, seizure occurrence, and neurobehavioural functioning. Secondary aims were to assess the effects of timing of the dose (eg, starting <4 h *vs* 4–8 h after injury), sex, and ethnic origin and to determine the rate of treatment-associated adverse events.

Methods

Participants

Patients with moderate to severe traumatic brain injury who were admitted to Harborview Medical Center, Seattle, WA, USA (a level 1 regional trauma centre), between August, 1998, and October, 2004, were eligible for the study. Moderate to severe traumatic brain injury was defined as: the need for intracranial surgery within 8 h of injury; a post-resuscitation Glasgow coma scale[12] (GCS) score of 3–12; or, if intubated, a GCS motor score of 1–5 without pharmacological paralysis. We classified intracranial surgery as being a craniectomy, craniotomy, or elevation of depressed fracture with dural repair, but not placement of burr or twist drill holes or the placement of intracranial pressure devices (including ventriculostomies). Patients were excluded if they were younger than 14 years, could not receive study drug within 8 h of injury, had serum creatinine concentrations more than 177μmol/L, were pregnant, were prisoners, or were known to live overseas.

The protocol and procedures were approved by the University of Washington Human Subjects Division. The study was permitted to enrol patients with waiver of consent under the regulation for emergency medical research.

Procedures

Patients were treated in a consistent manner over the course of the trial. Initial treatment in the emergency room, operating theatre, intensive care unit, and other wards was prescribed according to head-injury guidelines.[13] All patients were ultimately admitted to and cared for by the neurosurgery service under the direct supervision of a limited number of faculty attending physicians. There were established treatment guidelines, including indications for surgery, treatment of increased intracranial pressure, and other medical treatments, which did not vary among the attending neurosurgeons.

The study was a single-centre, randomised, parallel-group, double-blind trial (figure 1). Randomisation was stratified by severity (moderate: GCS total 9–12 or motor score 4–5 *vs* severe: GCS total 3–8, or motor score 1–3, or pharmacologically paralysed with intracranial surgery) and by age (≤40 years *vs* >40 years). Randomisation was blocked with block sizes of two or four to ensure balance. A member of the neurosurgery biostatistical unit (JB) created a computer-generated list, which was kept in the restricted area of the pharmacy. After enrolling the participant, the research nurse called or faxed the order sheet to the pharmacist to randomly assign a patient to a treatment group. When the study nurse sent the order sheet for a new patient, the pharmacist wrote the person's name on the next line of the appropriate sheet and prepared the active drug or placebo as indicated for administration. Participants, doctors and nurses treating them, research nurses, and those involved with the assessment of outcome were all masked to treatment assignment. There was no formal assessment of the success of the masking.

The intervention consisted of an initial intravenous loading dose of magnesium sulfate or identical-appearing saline given over 15 min within 8 h of injury and followed by a continuous infusion to maintain magnesium concentrations in the target range for

***Panel:* Measures included in the composite outcome analysis**

Composite outcome measures
Survival time (censored at 6 months)
Time to early seizures—ie, seizures occurring after randomisation but by day 7 after injury
Time to late seizures—ie, seizures occurring after day 7 after injury, (censored at 6 months)
Glasgow coma scale (at 1, 3, and 6 months)

Neuropsychological measures (all at 6 months)
Wechsler abbreviated scale of intelligence full scale IQ
Wechsler adult intelligence scale-third edition processing speed index
Selective reminding test sum of recall
Selective reminding test 30 min delay
Paced auditory serial addition test (PASAT) sum of correct
Trail making test Part A and B (time to complete)
Finger tapping test dominant and non-dominant hand
Grooved pegboard test dominant and non-dominant hand
Controlled oral word association test (COWAT)
Stroop test part I and II
Kimura memory for designs test immediate recall
Kimura memory for designs test 30 min delay recall
Galveston orientation and amnesia test (also at 1 and 3 months)

Functional status measures
Functional status examination (at 3 and 6 months, also separately by family member or friend at 6 months)
Glasgow outcome scale-extended (at 1, 3, and 6 months)
Medical outcomes study 36-item short-form health survey (SF-36) physical (at 6 months)

Other measures
Symptom checklist (at 6 months)
Cognitive questionnaire (at 6 months)
Living situation (at 1, 3, and 6 months)
Resumption of primary role activity (at 3 and 6 months)

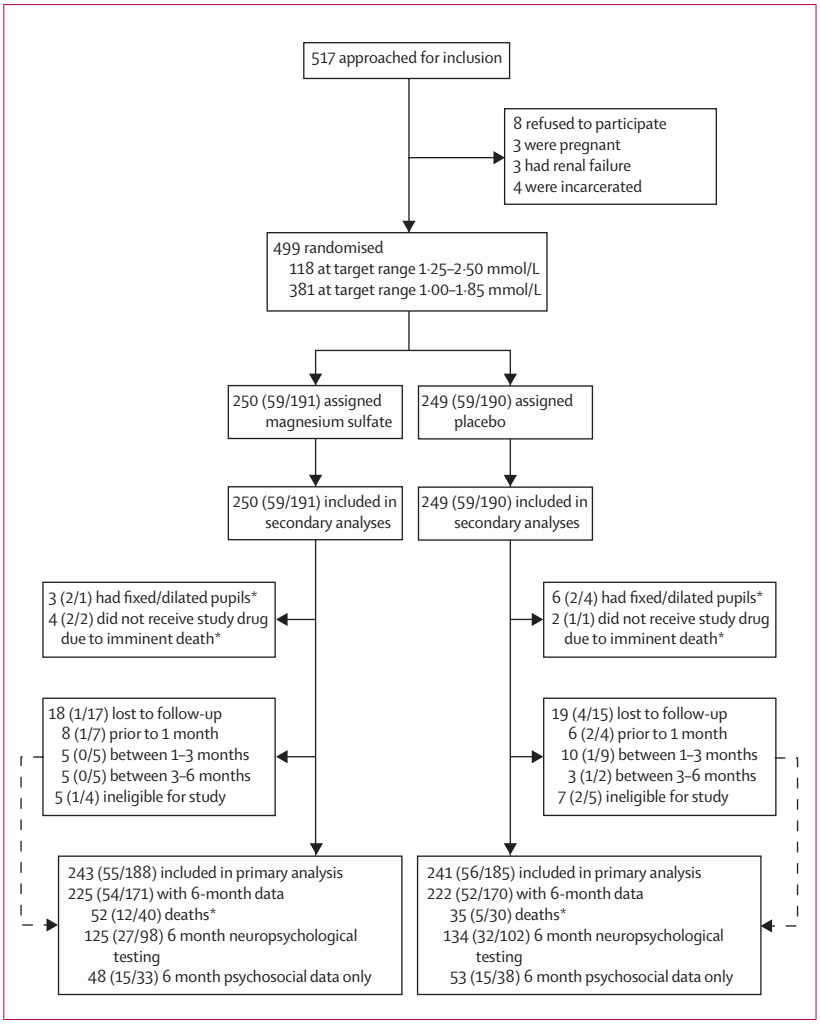

***Figure 2*: Trial profile**
Numbers in parentheses break down the total into cases in the 1·25–2·5 mmol/L and 1·00–1·85 mmol/L target range groups. *Deaths were regarded as having full neuropsychological data at 6 months.

5 days. For the first 118 patients, the target range was 1·25–2·5 mmol/L with a loading dose of 0·425 mmol/kg followed by the initial infusion of 0·10 mmol/kg/h.

The normal range of total magnesium is 0·75–1·0 mmol/L. Because of concerning trends in deaths and blood pressure noted at the first of the protocol-specified annual safety analyses, the study was restarted with a lower target range of 1·0–1·85 mmol/L achieved by a loading dose of 0·30 mmol/kg followed by an initial infusion of 0·05 mmol/kg/h. The research pharmacist adjusted the infusion rate daily according to an algorithm based on the magnesium concentration that day and the target level. Clinicians were not allowed to order any tests of magnesium concentration during the infusion or for 2 days after it ended; they monitored calcium clinically. Based on a pilot study we conducted, the initial serum target range went up to the highest magnesium concentration that could be maintained without the need for excessive calcium supplementation, which would compromise blinding. The choice of the lower target range was based on a promising human head injury pilot study,[14] which showed improved functional outcome without any side-effects, a preclinical head injury study,[10] clinical cardiac studies,[15,16] and a pilot stroke study.[17] This range approximates the serum concentrations attained in the higher dose positive animal studies.[10]

Consistent with the standard of care, the study pharmacist ordered a bolus of magnesium for the placebo-assigned cases if serum magnesium was below normal (0·75 mmol/L); saline was given in some cases in the magnesium group to maintain blinding.

The primary outcome was a composite based on 39 individual measures including mortality, seizures,

and health-status measures, assessed by telephone at 1 and 3 months and as part of a formal in-person, comprehensive examination at 6 months that included neuropsychological testing (panel). A family member or someone else who knew the participant well before and after the injury also assessed the participant's health status at the 6 month test. To enhance data quality, outcome examiners were extensively trained in standard test administration and all scoring was checked by a second examiner.

The composite outcome was the average across measures of the rank (expressed as a percentage) of the patient on each measure.[18] Deaths were assigned the worst score on neuropsychological measures, and patients who were too neurologically impaired to perform the neuropsychological tests were scored just above deaths. The outcomes were not explicitly weighted in forming the composite, so functioning at 6 months (especially neuropsychological test scores), when most outcomes were obtained, received a heavy weight.

Statistical analysis

The protocol specified a sample size of 400 (200 per group). Simulations showed that this sample size gave

	Target range 1·25–2·5 mmol/L		Target range 1·0–1·85mmol/L		Combined sample	
	$MgSO_4$ (n=59)	Placebo (n=59)	$MgSO_4$ (n=191)	Placebo (n=190)	$MgSO_4$ (n=250)	Placebo (n=249)
Age						
Mean age, years (SD)	34·7 (14·9)	36·2 (18·3)	34·1 (17·1)	33·9 (17·6)	34·3 (16·6)	34·4 (17·8)
Age ≤40 years	37 (63%)	39 (66%)	131 (69%)	137 (72%)	168 (67%)	176 (71%)
Age >40 years	22 (37%)	20 (34%)	60 (31%)	53 (28%)	82 (33%)	73 (29%)
Sex						
Male	45 (76%)	46 (78%)	145 (76%)	145 (76%)	190 (76%)	191 (77%)
Female	14 (24%)	13 (22%)	46 (24%)	45 (24%)	60 (24%)	58 (23%)
Ethnic origin						
Non-Hispanic white	45 (76%)	50 (85%)	144 (75%)	144 (76%)	189 (76%)	194 (78%)
Minority group	14 (24%)	9 (15%)	47 (25%)	46 (24%)	61 (24%)	55 (22%)
Injury severity						
Mean GCS before load (SD)	7·3 (2·9)	7·0 (3·0)	7·1 (2·8)	7·1 (2·8)	7·2 (2·8)	7·1 (2·9)
Severe injury*	24 (41%)	29 (49%)	68 (36%)	77 (41%)	92 (37%)	106 (43%)
Moderate injury	35 (59%)	30 (51%)	123 (64%)	113 (59%)	158 (63%)	143 (57%)
CT abnormalities and other injury characteristics						
Cortical contusions	33 (56%)	33 (56%)	117 (61%)	108 (57%)	150 (60%)	141 (57%)
Subdural haematoma	35 (59%)	33 (56%)	105 (55%)	84 (44%)	140 (56%)	117 (47%)
Evacuated subdural haematoma	16 (27%)	10 (17%)	32 (17%)	25 (13%)	48 (19%)	35 (14%)
Epidural haematoma	12 (20%)	14 (24%)	41 (21%)	28 (15%)	53 (21%)	42 (17%)
Evacuated epidural haematoma	8 (14%)	8 (14%)	30 (16%)	15 (8%)	38 (15%)	23 (9%)
Intracerebral haematoma	7 (12%)	8 (14%)	16 (8%)	25 (13%)	23 (9%)	33 (13%)
Depressed skull fracture	11 (19%)	13 (22%)	35 (18%)	35 (18%)	46 (18%)	46 (19%)
Penetrating brain injury	4 (7%)	2 (3%)	8 (4%)	9 (5%)	12 (5%)	11 (4%)
Diffuse axonal injury	18 (31%)	14 (24%)	72 (38%)	68 (36%)	90 (36%)	82 (33%)
Immediate seizures before randomisation	9 (16%)	13 (24%)	13 (7%)	22 (12%)	22 (9%)	35 (15%)
Bilateral non-reactive pupils	15 (26%)	11 (20%)	30 (16%)	34 (19%)	45 (18%)	45 (18%)
Mean AIS head (SD)	4·7 (0·6)	4·6 (0·5)	4·6 (0·6)	4·5 (0·7)	4·7 (0·6)	4·5 (0·6)
Maximum AIS excluding head (SD)	2·1 (1·3)	2·1 (1·5)	2·4 (1·2)	2·4 (1·3)	2·3 (1·2)	2·3 (1·4)
Mechanism of injury						
Motor vehicle	25 (42%)	30 (51%)	100 (52%)	96 (51%)	125 (50%)	126 (51%)
Fall	15 (25%)	13 (22%)	33 (17%)	42 (22%)	48 (19%)	55 (22%)
Violence	9 (15%)	8 (14%)	24 (13%)	24 (13%)	34 (14%)	32 (13%)
Other	10 (17%)	8 (14%)	34 (18%)	28 (15%)	44 (18%)	36 (15%)
Systolic blood pressure before dosing (SD)	124 (25)	127 (21)	129 (22)	129 (20)	128 (23)	129 (20)
Diastolic blood pressure before dosing (SD)	76 (18)	77 (17)	77 (16)	76 (15)	77 (17)	77 (16)

Data are number (%) or mean (SD). $MgSO_4$=magnesium sulfate. GCS=Glasgow coma scale. AIS=abbreviated injury scale. *Severe injury defined as: non-intubated with GCS 3–8; intubated with GCS motor score 1–3; or paralysed and emergent craniotomy. Age-group and severity group are based on verified information which may differ from that used for randomisation.

Table 1: **Characteristics of the patients assigned to each treatment and their injuries**

at least 95% power to detect an increase of 10 percentage points on the dichotomised Glasgow outcome scale for severely injured participants; and similar improvement on other outcome measures and for cases with moderate severity. For categorical outcomes, similar improvement was defined as the same effect on the logistic scale. For continuous outcomes, it was defined as an additive effect equal, on average, to the same percent reduction in the deficit of those with similar brain injury severity compared with patients whose trauma did not affect the head. Because deaths and patients too neurologically impaired to be tested would not improve their scores with treatment (although the effect on categorical variables decreased their number), the actual additive effect for tested cases was adjusted to yield the desired average effect.

The protocol-specified primary analysis was a blocked Wilcoxon rank sum test[19] on the composite outcome with blocking on the four strata by three data completeness groups (lost to follow-up before 6 months *vs* 6 month information without neuropsychological testing *vs* full 6 month information including deaths and those too neurologically impaired for formal testing). The primary analysis excluded cases who had fixed and dilated pupils just before initial dosing or who died before receiving any study drug. For the remaining cases, the analysis was done according to the intention-to-treat principle for the different dose groups separately. One interim efficacy analysis was specified when approximately half of the cases had passed the time of the 6 month assessment. The interim analysis used O'Brien-Fleming[20] stopping boundaries, leaving a nominal two-sided significance level of 0·048 for the primary analysis. A futility analysis was specified to stop the trial if the conditional power was under 10% assuming the treatment effect used in the assessment of power.

Secondary analyses were by intention to treat on the composite and on individual measures. Cox regression[21] was used for comparing survival and time to early or late seizures.

	Target range 1·25–2·5 mmol/L						Target range 1·0–1·85 mmol/L					
	$MgSO_4$		Placebo		95% CI for difference	p/favours	$MgSO_4$		Placebo		95% CI for difference	p/favours
	n	Mean (SE)	n	Mean (SE)			n	Mean (SE)	n	Mean (SE)		
Primary analysis												
Excluding fixed and dilated pupils or not loaded	55	55 (4)	56	52 (4)	(–7 to 14)	0·70/M	188	48 (2)	185	54 (2)	(–10·5 to –2)	0·007/P
Secondary analyses												
Intention to treat (all randomised cases)*	59	51 (4)	59	50 (4)	(–7 to 11)	0·85/M	191	47 (2)	190	52 (2)	(–10 to –1·5)	0·01/P
Subgroup analyses												
Age												
Age ≤40 years	37	52 (5)	39	57 (5)	(–19 to 4·5)	0·33/P	131	53 (2)	137	57 (2)	(–12 to –1·5)	0·02/P
Age >40years	22	50 (7)	20	35 (4)	(–2 to 35·5)	0·11/M	60	35 (3)	53	41 (4)	(–12 to 2·5)	0·25/P
Severity												
Severe†	24	40 (6)	29	40 (5)	(–10 to 21·5)	0·62/M	68	29 (3)	77	45 (3)	(–21·5 to –5·5)	0·001/P
Moderate	35	59 (5)	30	59 (5)	(–17·5 to 13)	0·86/P	123	57 (2)	113	58 (3)	(–7 to 4·5)	0·50/P
Emergent intracranial surgery												
No	30	57 (6)	36	52 (5)	(–24 to 8·5)	0·53/P	125	49 (2)	134	54 (3)	(–12 to –1·5)	0·02/P
Yes	29	45 (5)	23	46 (6)	(–17 to 19)	0·69/M	66	44 (4)	56	49 (4)	(–13 to 3)	0·35/P
Sex*												
Male	45	52 (5)	46	53 (5)	(–10·5 to 11)	0·96/P	145	50 (2)	145	53 (2)	(–12 to –2·5)	0·007/P
Female	14	49 (10)	13	37 (6)	(–12·5 to 28·5)	0·87/M	46	40 (4)	45	49 (4)	(–12 to 8)	0·78/P
Ethnic origin*												
Non-Hispanic white	45	54 (5)	50	51 (4)	(–6·5 to 16)	0·64/M	144	47 (2)	144	51 (2)	(–9 to 0·5)	0·11/P
Minority group	14	42 (8)	9	45 (7)	(–44 to 32)	0·93/M	47	47 (4)	46	56 (4)	(–22·5 to –4·5)	0·01/P
Time from injury to study drug*												
Loaded ≤4 h	13	50 (9)	11	40 (10)	(–6·5 to 50)	0·07/M	35	41 (5)	32	48 (5)	(–17 to 2·5)	0·11/P
Loaded >4 h	44	54 (5)	47	53 (4)	(–17 to 8·5)	0·64/P	153	49 (2)	156	54 (2)	(–10·5 to –0·5)	0·03/P
Baseline serum magnesium												
Below lower limit of normal	26	49 (7)	30	51 (5)	(–25·5 to 16)	0·55/P	116	46 (2)	107	52 (3)	(–13 to 0)	0·06/P
At least normal	28	54 (5)	24	54 (6)	(–19·5 to 13)	0·56/P	62	51 (4)	74	54 (3)	(–14 to 5)	0·21/P

Higher values indicate better outcome. Positive values of the CI endpoints represent better outcome for those assigned magnesium. $MgSO_4$=magnesium sulfate. M=magnesium sulfate. P=placebo. *Protocol-specified secondary analysis. †Severe injury defined as: non-intubated with GCS 3–8; intubated with GCS motor score 1–3; or paralysed and emergent craniotomy.

***Table 2*: Results on the composite outcome, by average percentile rank**

Confidence intervals were calculated by direct enumeration with deaths assumed not to change neuropsychological test scores. Subgroups were examined with blocked Wilcoxon tests on the composite. For analyses within subgroups with fewer than 50 participants, age-group was not used as a blocking factor. The measures were not weighted in forming the composite. If there were no missing data, the composite would be the average over measures of the rank within measure, converted to a percent by subtracting 0·5, dividing by the sample size, and multiplying by 100. This trial is registered with ClinicalTrials.gov, number NCT00004730.

Role of the funding source

The sponsor of the study, the National Institutes of Health, National Institute of Neurological Disorders and Stroke, appointed the NIH Data and Safety Monitoring Board but had no members on that Board. The sponsor had no direct role in study design, data

	Target range 1·25–2·5 mmol/L						Target range 1·0–1·85 mmol/L					
	$MgSO_4$		Placebo		Test for treatment effect		$MgSO_4$		Placebo		Test for treatment effect	
	n	Data	n	Data	95% CI for ratio or difference	p*/favours	n	Data	n	Data	95% CI for ratio or difference	p*/favours
Individual outcome measures												
Mortality†	59	0·28 (0·06)	59	0·14 (0·05)	(1·00 to 5·50)	0·05/P	191	0·24 (0·03)	190	0·20 (0·03)	(0·87 to 2·10)	0·18/P
Early seizures†	58	0	58	0	..	..	182	0·01 (0·01)	183	0	(0·00 to ∞)	0·62/P
Late seizures†	47	0·17 (0·06)	50	0·13 (0·05)	(0·47 to 4·27)	0·53/P	154	0·09 (0·03)	165	0·06 (0·02)	(0·45 to 2·89)	0·79/P
Glasgow outcome scale extended at 6 months	57	4·7 (0·4)	54	4·7 (0·3)	(–1·0 to 0·9)	0·80/P	176	4·2 (0·2)	174	4·5 (0·2)	(–1·0 to 0·0)	0·08/P
Functional status examination at 6 months‡	50	19·3 (1·4)	44	17·9 (1·5)	(–3·0 to 10·5)	0·45/P	163	19·4 (0·8)	154	17·7 (0·9)	(–0·0 to 7·9)	0·05/P
Full scale intelligence quotient§	42	91 (4)	36	95 (4)	(–49 to 3·0)	0·08/P	140	89 (2)	124	92 (2)	(–18·9 to –0·9)	0·04/P
Processing speed index§	42	84 (3)	41	82 (3)	(–30·9 to 5·0)	0·20/P	143	81 (2)	137	82 (2)	(–18·9 to –0·1)	0·03/P
Selective reminding (sum of recall)§	42	66 (4)	35	62 (6)	(–37 to 7·9)	0·24/P	139	63 (3)	124	65 (3)	(–17 to –0·1)	0·05/P
Trails A (sec)‡§	44	40 (5)	41	47 (5)	(–9·0 to 35·9)	0·54/P	146	44 (3)	137	47 (3)	(–1·0 to 13·9)	0·11/P
Trails B (sec)‡§	44	112 (14)	40	135 (18)	(–24 to 87)	0·37/P	144	125 (9)	136	132 (10)	(–1·0 to 42)	0·07/P
Finger tapping (dominant hand)§	42	46 (3)	39	42 (3)	(–28 to 6·9)	0·44/P	145	40 (2)	136	39 (2)	(–8·9 to 2·0)	0·34/P
Physiological measures												
Systolic BP	55	127 (2)	56	134 (2)	(–12 to –2)	0·01/P	184	134 (1)	184	132 (1)	(0 to 5)	0·10/M
Systolic BP ever <90	55	21 (36%)	56	15 (26%)	(–8 to 27)	0·32/P	184	67 (36%)	184	60 (32%)	(–7 to 13)	0·51/P
Diastolic BP	55	70 (1)	56	74 (1)	(–6 to –1)	0·01/P	184	72 (1)	184	73 (1)	(–2 to 1)	0·49/P
Diatolic BP ever <50	55	37 (64%)	56	25 (44%)	(1 to 37)	0·04/P	184	119 (64%)	184	117 (63%)	(–10 to 10)	1·00/P
ICP	53	15 (1)	52	15 (1)	(–3 to 4)	0·69/M	171	16 (1)	164	16 (1)	(–1 to 2)	0·84/P
ICP ever >20	53	41 (71%)	52	42 (74%)	(–20 to 14)	0·84/M	171	150 (80%)	164	139 (75%)	(–4 to 14)	0·26/P
CPP	53	74 (2)	52	79 (1)	(–10 to –2)	0·01/P	171	76 (1)	164	77 (1)	(–3 to 2)	0·54/P
CPP ever <60	53	38 (66%)	52	32 (56%)	(–9 to 27)	0·34/P	171	133 (71%)	164	121 (65%)	(–4 to 15)	0·27/P
Medical complications within 1 week												
Atelectasis	59	32 (54%)	59	35 (59%)	(–24 to 13)	0·71/M	191	137 (72%)	190	125 (66%)	(–4 to 15)	0·23/P
Hypotension	59	35 (59%)	59	26 (44%)	(–4 to 33)	0·14/P	191	120 (63%)	190	114 (60%)	(–7 to 13)	0·60/P
Pulmonary oedema	59	17 (29%)	59	17 (29%)	(–17 to 17)	1·00/..	191	78 (41%)	190	61 (32%)	(–1 to 19)	0·09/P
Pneumonia	59	10 (17%)	59	12 (20%)	(–19 to 12)	0·81/M	191	37 (19%)	190	37 (19%)	(–8 to 8)	1·00/M
Respiratory failure	59	2 (3%)	59	3 (5%)	(–12 to 9)	1·00/M	191	25 (13%)	190	14 (7%)	(–1 to 12)	0·09/P
Adult respiratory distress syndrome	59	2 (3%)	59	5 (8%)	(–16 to 6)	0·44/M	191	16 (8%)	190	16 (8%)	(–6 to 6)	1·00/P

Data are estimated cumulative incidence from Kaplan-Meier curve (SE), mean (SE), or count (%). $MgSO_4$=magnesium sulfate. BP=blood pressure. ICP=intracranial pressure. CPP=cerebral perfusion pressure. *Significance level from Cox regression for mortality and seizures, blocked Wilcoxon for other outcome measures, *t*-tests for continuous physiologic measures and Fisher's exact tests for dichotomous variables. †Confidence interval is for the hazard ratio for those assigned magnesium to those assigned placebo, so ratios greater than 1 indicate a higher risk of death or seizure in the magnesium group. Point estimates are 2·22 and 1·33 for mortality in the higher and lower dose groups and 1·37 and 1·12 for late seizures. Participants with pre-injury seizures were excluded from the seizure outcome analyses and those who died before day 8 are excluded from the late seizure outcome analysis. ‡Lower value indicates better performance. Negative values of the confidence interval endpoints represent better outcome for those assigned magnesium. §Neuropsychological measures exclude deaths for mean and SE estimates, but include them with the worst rank for the significance tests.

Table 3*: Results on selected individual measures of outcome, physiology, and adverse events

collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The initial (higher) dose was at the suggestion of the grant review study section. The corresponding author and biostatisticians had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

499 patients were randomly assigned to a study group, 49% of whom under waiver of consent. Only eight families (<2%) refused consent for the study before randomisation. Overall, 93% were followed up through 6 months, including 72% with full neuropsychological data at the 6 month assessment (figure 2).

Baseline characteristics were quite well balanced between the treatment and the placebo groups (table 1). However, consistent with the epidemiology of traumatic brain injury most patients were young men; the range of ethnic origins was similar to that of western Washington; and most patients were randomised in the moderate injury stratum. Additionally, the group assigned magnesium at the lower target range and the combined sample had more patients with haematomas and with worse abbreviated-injury-scale-head scores. Average time from injury to initial study drug bolus was 5·4 h (SD 1·5). Study drug was given for the duration specified in the protocol to 95% of cases, including 5% who were discharged before 5 days and 9% who died. 25 patients stopped taking the study drug before 5 days—nine because of intravenous problems, seven because of an error, and nine for other or for unspecified reasons. Average total magnesium concentrations were 2·15 mmol/L (SD 0·35) in the higher magnesium target group, 1·45 mmol/L (SD 0·2) in the lower magnesium target group, and 0·9 mmol/L (SD 0·1) in the placebo group. For ionised magnesium, the values were 1·35 mmol/L (SD 0·2), 1·0 mmol/L (SD 0·15), and 0·55 mmol/L (SD 0·08) in the higher, lower, and placebo groups, respectively.

Masking was broken in 40 (8%) cases, primarily when a clinician ordered magnesium as part of a routine laboratory test. The research nurse became aware of the study treatment in 4% of cases; the patients and outcome examiners remained consistently unaware of the assigned treatment group.

The primary analysis excluding predosing deaths or those with fixed dilated pupils revealed that magnesium showed no positive effect at either target concentration (table 2). In fact, with a two-sided test, the primary analysis and the secondary standard intent-to-treat analysis at the lower magnesium target concentration were significant in the direction of those assigned to magnesium doing less well overall. In the higher magnesium group, the treatments did not differ. Those assigned to the higher concentration of magnesium did slightly better in about half of the subgroups (table 2). Unfortunately, in the larger study with the lower magnesium target concentration, none of these trends held up and in every subgroup, those assigned to magnesium had at least a slightly worse outcome.

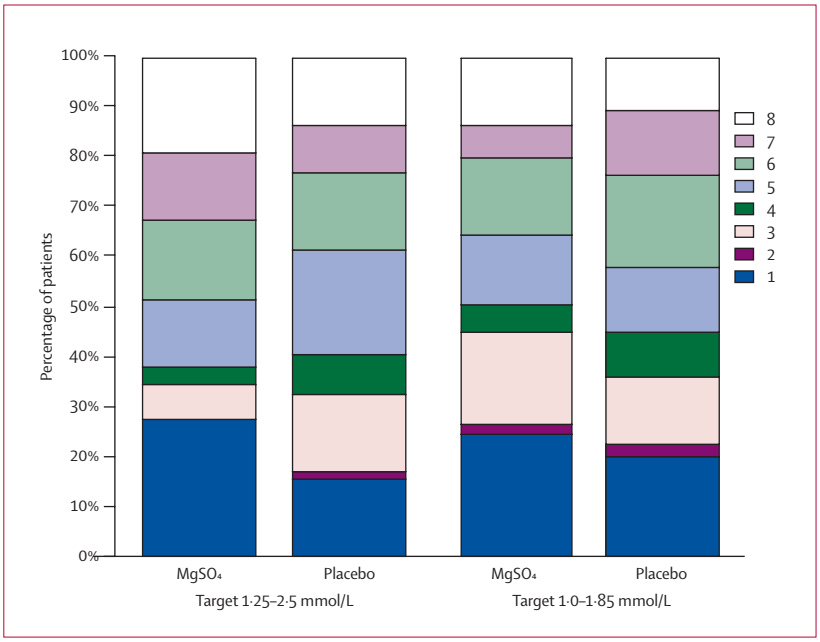

***Figure 3*: Glasgow outcome scale-extended (GOSE) at 6 months by target level and treatment**
1=death; 2=vegetative state; 3=lower severe disability; 4=upper severe disability; 5=lower moderate disability; 6=upper moderate disability; 7=lower good recovery; 8=upper good recovery.

There was no suggestion of a positive effect in any outcome area assessed. Table 3 lists a few of the measures for illustrative purposes. At the high magnesium target concentration, the mortality rate for the magnesium cases was double that for placebo. The mortality ratio decreased to 1·2 at the lower target level. Early seizures were rare as 96% of participants received phenytoin for the first week as part of their clinical care. Magnesium showed no positive effect on prevention of late epileptic seizures. The neuropsychological measures shown examine attention (trail tests A and B[22]), information processing speed (WAIS PSI[23]), memory (SR[24]), an estimate of overall intellectual functions (WASI FSIQ[25]), and motor speed (finger tapping speed[22]). The functional status examination (FSE[26]), a detailed summary of functioning in everyday life, yielded similar results. Figure 3 shows the Glasgow outcome scale-extended scores for each group.[27]

Blood pressure and cerebral perfusion pressure (intracranial pressure minus mean arterial blood pressure) were lower in the high magnesium group during the treatment period (table 3). This result, along with the upward trend in mortality, lowered the target magnesium concentration. At the lower magnesium target concentration, magnesium had no effect on blood pressure and cerebral perfusion pressure. Mortality was

the main serious adverse event. Other major medical complications were similar between groups, except for a slight excess of pulmonary oedema and respiratory failure in the lower magnesium target group.

Discussion

Consistent with a large trial in stroke,[28] our findings do not lend support to the hypothesis that magnesium treatment would improve outcome after traumatic brain injury in human beings. However, whether these negative results might be associated with inadequate power should be considered. Simulations show that our study had more than 80% power to detect a percentage point difference of 10 between the treatment and placebo groups in dichotomised Glasgow outcome scale-extended scores for severely injured patients when all measures and moderately injured patients were assumed to have a similar effect either on a logit scale for categorical outcomes or on a percent reduction in deficit for continuous outcomes. The fact that the primary analysis reached significance, albeit in the direction indicating an adverse effect of magnesium, attests to the sensitivity of the measures and analysis and the adequacy of the sample size. Those receiving magnesium at the highest dose had lower blood pressure than did those in the other groups, which could have had an adverse effect on outcome; however, the lowest dose of magnesium had no effect on blood pressure or cerebral perfusion pressure. Failure of the randomisation procedures and protocol violations are not likely explanations of the negative effect since there were few protocol violations and there was no evidence of the randomisation process being compromised.

We did additional regression analyses adjusting for any baseline variables imbalanced (at $p<0\cdot1$) in either dose group. With the adjustment, magnesium looked better, but in the lower dose group the p value was still $0\cdot09$ in favour of placebo. Moreover, we did not note any significantly positive treatment effects in any of the subgroup analyses. Almost all patients were given phenytoin for the first week, which would have lessened any possibility of seeing an effect of magnesium on early seizures. No laboratory work has looked at an interaction between magnesium and phenytoin, but a huge interaction would be needed to bring a study from significant in one direction to significant in the other.

Generalisability of results is always an issue with single centre trials. Although the participants were treated by a limited number of attending neurosurgeons, other factors suggest good generalisability. Harborview is the only level 1 trauma centre in the state and almost all patients with severe traumatic brain injury from a multi-state region are brought there. Very few families or patients refused consent or withdrew consent and follow-up was 93%. Patients were not enrolled if, before randomisation, there was a decision to give only comfort care. Although residents sometimes forgot to call the research nurses about potentially eligible cases, the only obvious pattern is unlikely to limit generalisability—missed cases increased when the clinical service was especially busy.

Our primary outcome was a composite based on survival, seizures, measures of functional status, and a well validated comprehensive battery of neuropsychological tests known to be sensitive to the integrity of the brain. This comprehensive measurement of outcome had a high probability of detecting a consistent positive effect of treatment. Analyses of individual outcomes showed the same trend as the composite. The composite primary endpoint is uncommon in clinical trials. The additional sensitivity conferred by the composite endpoint allowed this trial, with under 400 moderately or severely injured participants, a power similar to that of a study of 900 participants with the more commonly used primary outcome dichotomised Glasgow outcome scale. Biegon[29] suggested that neuroprotective drugs could accelerate recovery, but despite repeated measurement of outcome over the initial 6 month period post trauma, we were unable to document a difference at any time.

As with any clinical trial, this study tested only a few of the possible combinations of dose, start time, and duration of treatment. A different choice of one or more of these could have yielded a beneficial effect. However, the choices used in this trial were within the range used in positive preclinical studies. Furthermore, subgroup analyses looking at start time and dose at least gave no hint that variation of these components within the range observed would have yielded more positive results for the intervention. For example, even the subgroup started within 4 h (generally between 2 h and 4 h) showed no positive effect of magnesium at the lower dose (table 2).

Unlike in most of the positive animal studies, we used a continuous infusion of magnesium to maintain consistent levels. These consistently high magnesium concentrations might actually have a negative effect on recovery. Data[29] have shown that hyperactivity of the glutamate NMDA receptor occurs within the first hour after experimental brain injury, but that stimulation of NMDA receptors at 24 h and 48 h after injury improves outcome. Continuous high concentrations of magnesium in this subacute period would attenuate this NMDA stimulation and plausibly adversely affect recovery. Also, by contrast with early preclinical studies showing a broad efficacy of magnesium sulfate observed early after experimental brain injury, a more recent study[30] did not find a positive effect on cognitive performance when animals were studied 8 months after injury, despite a significantly reduced hippocampal tissue loss.

Although we successfully achieved our target serum level goals, we might not have substantially increased magnesium concentrations in the CNS. McKee and

colleagues[31] described the function of the blood–brain barrier in patients with traumatic brain injury by using magnesium sulfate infusions initiated an average of 5 days after injury (range 1–16 days). These investigators showed that increasing serum magnesium concentrations yielded only a marginal increase in CSF concentrations (total and ionised); they concluded that the regulation of the blood–brain barrier for magnesium remains largely intact after brain injuries. Their conclusion, however, might not apply to the present study because we started magnesium treatment within hours (mean 5·4 h, SD 1·5) of the initial event. Disruption of the blood–brain barrier is commonly observed shortly after experimental and clinical traumatic brain injury.[32] In rat models of traumatic brain injury, intravenous administration of magnesium 30 min post injury has been shown to result in significant increases in intracellular free magnesium brain concentrations compared with in non-treated controls.[33] Increases in brain concentrations were linearly correlated with magnesium dose and neurological outcome as determined by the rotorod test.[34,35]

Consistent with the findings in the laboratory, about 60% of participants had a magnesium concentration below the lower limit of normal before study drug loading. 85% of cases in the placebo group had at least one magnesium concentration below the normal range. Conceivably, supplementation of magnesium as part of standard care might be sufficient to obtain the beneficial effect of magnesium.

In summary, we undertook a double-blind, single-institution trial designed to test the hypothesis that magnesium supplementation given within 8 h of significant head injury would attenuate mortality and improve functioning. By using a broad array of measures, we did not prove our hypothesis. Although Virchow in 1880 stated that "the absence of proof does not constitute the proof of absence", we would nevertheless conclude that there is no clinical suggestion that these regimens of magnesium are useful in the treatment of moderate or severe head injuries.

Contributors

HRW, NRT, SDD, GDA, and DWN conceived, designed, and obtained funding for the study. HRW and NRT were principal investigators. NRT, SDD, and GDA provided study supervision. NRT and JB were the study statisticians. PNM and JEM oversaw acute aspects and follow-up for the study. GWB, JS, and TL were local safety monitors. HRW, RGE, GWB, and DWN provided clinical support. NRT, HRW, GDA, and SDD drafted the manuscript, which all authors subsequently reviewed, edited, and approved.

Conflicts of interest

We have no conflicts of interest.

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